REMARKS

Claims 1, 2-9, 11-24, 26, 28 and 30-31 are pending in the case. Claims 16, 17 and 30 have been withdrawn from examination. Claim 15 has been objected to. New claim 31 has been deemed allowable. Claims 2, 10, 25, 27 and 29 have been canceled. Withdrawn claims 16, 17 and 30 have also been canceled. The other claims have been rejected.

Rejection Under 35 U.S.C. §112

Claims 2-11, 25, 27 and 29 have been rejected under section 112, second paragraph, as indefinite for use of the term "bipolar" in reference to primer P2. In response, claims 2, 25, 27 and 29 have been canceled and claim 1 has been amended to incorporate the limitations of claim 2 verbatim except that the term "bipolar" has been deleted and replaced by the requirement that P2 support rolling circle amplification (as described in Figures 1 and 2 of the application). In addition, claims 3, 4, 8 and 11 have been amended to depend from claim 1 instead of claim 2.

Rejection Under 35 U.S.C. §102

Claims 1 and 12-14 were rejected under section 102(b) as anticipated by Valimaa et al (1998). Applicant responds that, in order to anticipate a claim, the reference must disclose each limitation of the claim. Claim 1 has been amended to recite that the hybridization of P2 to extended P1 is determined using rolling circle amplification and it is conceded in the Office Action (at page 5, at line 6 from the bottom) that Valimaa does not teach use of rolling circle amplification. Thus, amended claim 1, as well as claims 12-14 that depend therefrom, are not anticipated by Valimaa et al.

Rejection Under 35 U.S.C. §103(a)

Claims 1-14 and 18-25 were rejected as obvious over Valimaa et al (1998) in view of Chee et al (U.S. Patent 6,355,431).

Applicant responds that claim 1, as amended, and the remaining claims that depend from claim 1, either directly or indirectly, are not rendered obvious by these references, either alone or in combination.

The rejection recites claim limitations derived from Valimaa to the point of using rolling circle amplification (RCA) and then relies on Chee et al to supply the RCA step previously recited in claim 2. However, no mention is made in the Office action of how to combine these references to achieve the claimed invention. Instead, there is a piecemeal description of the steps of the claimed process, each coming from a different reference and these are then tied together with the conclusory statement that it would have been obvious to combine them. Applicant responds that these references cannot be combined.

Valimaa et al relies on use of the polymerase chain reaction (PCR) to amplify a specific allele (which is not necessarily a single base polymorphism (SNP) although the rejection equates alleles and SNPs). In fact, Valimaa makes no mention of SNPs. The rejection then relies on Chee et al as teaching the desirability of RCA as a means of amplification.

In general, where references are to be combined to show obviousness, one reference provides some missing part that, when added to the teaching of the other reference, achieves substantially the claimed invention. That does not occur here, nor can it occur.

Valimaa uses PCR as the method of amplifying a specific allelic sequence and

then uses a probe to detect the amplified sequence. Chee et al discloses single base extension using a terminating nucleotide so that only one base is added and only if this base is complementary to the corresponding base on the target strand (see column 16, lines 37-39, of Chee) and then amplifies using RCA, which is described as a ligation dependent procedure (see Chee et al at column 19, lines 20, 33 and 54). Thus, one would not expect to combine the RCA method described by Chee et al with the PCR procedure of Valimaa et al because both are methods of amplification and the Valimaa process does not provide for any ligation step that would provide an amplification target circle, thus making RCA difficult if not impossible in conjunction with Valimaa. Chee uses RCA to amplify a sequence after single base extension while in Valimaa the extended sequences have already been amplified by PCR. Further, Chee et al describe RCA as a method that occurs following a ligation step and the products of the PCR method of Valimaa et al leave nothing to be ligated (i.e., there are no adjacent primers, or primer termini, to be ligated).

Unlike Chee, Applicant teaches use of a preformed ATC that hybridizes to a primer P2 that is bound to an extended P1 (which extension either shows or does not show the presence of an SNP, depending on the P1 primer used) and wherein no additional ligation step is used. Avoidance of the need for any ligation step is a feature of Applicant's invention (see application at page 5, lines 11-14). Consequently, it is conceivable that one would be motivated to use Applicant's own RCA method in conjunction with Valimaa but that cannot be used against Applicant.

The rejection also relies on the Ishikawa et al (1995) paper as teaching the use of a one base mismatch to improve specificity. Applicant respectfully contends that there is no such motivation to combine these references because Ishikawa teaches a mismatch at the second position from the 3'-end (not positions 1 and/or 3 as in claim 1) to improve annealing during thermocycling (see page 316, column 2, paragraph beginning "Figure 2 shows..." and also see the description of Figure 2 on page 317). Conversely, Applicant is

not relying on a mismatch near the 3' terminus to increase the specificity of PCR amplification but to increase the specificity of primer extension (which determines allele discrimination) under isothermal conditions. In short, Ishikawa is irrelevant to any RCA method because RCA involves no thermocycling steps and therefore there is no motivation to combine Chee and Ishikawa.

Claim 18 (including claims dependent therefrom) is likewise not rendered obvious over these references because it relies on use of the method of claim 1, which is not obvious over these methods.

Claims 1-14 and 18-29 were also rejected based on the aforementioned references and also in view of Lizardi et al (1998). Here, the rejection relies on Lizardi's teaching regarding the RCA-CACHET method and use of a 3'-5'-3' primer. The rejection refers to the teaching of Figure 6 of Lizardi and states that Lizardi shows the use of such a primer in the RCA method of Chee. However, the method shown in Figure 6 (described in the legend as the "RCA-CACHET ligation dependent assay" again relies on ligation to determine whether amplification occurs or not. Applicant's method does not rely on ligation and claim 1 has been amended to make this clear.

Further, the 3'-5'-3' primer is ligated to the P1 primer and the resulting oligonucleotide is amplified by RCA. Such a primer could not be used in the method of Chee because in Chee the ATC is formed by ligation of the primer ends, or by ligation of adjacent primers, so that a bipolar primer is unnecessary and one would therefore not be motivated to use it. In Lizardi the adjacent primers form on the target sequence, are then ligated, the target removed and the ATC is bound to the ligated oligonucleotide. This does not work in Chee, which uses the adjacent primers to form the ATC whereas Lizardi uses them to bind the ATC and so, again, one is not motivated to combine these references. Lizardi simply does not teach use of such a primer in the way that it would be used by Applicant in the claimed invention (as in claim 3), or in Chee, where the ATC is formed by

ligation of the primers.

The Commissioner is authorized to charge payment of any additional filing fees required under 37 CFR 1.16 associated with this communication or credit any overpayment to Deposit Account No. 03-0678.

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